PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

First Appellant: AGEJAS-CHICHARRO, Francisco Javier — Art Unit: 1625

Serial No.: 10/598,512

Filed: March 9, 2005 — Examiner: Binta M. Robinson

PCT Nat'l Entry Date (if applicable): September 1, 2006

For: PYRIDYL DERIVATIVES AND THEIR USE AS MGLU5 ANTAGONISTS

Docket No.: X16538

APPEAL BRIEF FOR AGEJAS-CHICHARRO, et al.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants appeal from the final rejection dated January 25, 2010, of Claim 5 of this application.

Real Party in Interest

The Real Party in Interest of the present case is Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, 46285, as the inventors of the subject matter in the above-referenced application assigned in February and March of 2005 all inventions disclosed in the above referenced application to Eli Lilly and Company.

Related Appeals and Interferences

Appellants are aware of no other appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

Status of Claims

Claims 1, 2, 4, 5, 14, 17, 18, 21, 22 and 26 are pending in the application.

Claims 3, 6-13, 15, 16, 19, 20 and 23-25 were previously cancelled.

Claims 1, 2 and 4 are withdrawn as being directed to non-elected subject matter.

Claim 5 is rejected and on appeal.

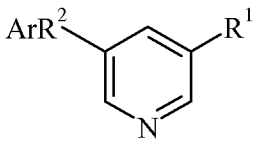
Claims 14, 17, 18, 21, 22, and 26 are objected to because they are based on a rejected claim.

Status of Amendments

No amendments have been filed subsequent to final rejection in the present case.

Summary of Claimed Subject Matter

Appellants' invention relates to certain pyridyl compounds as antagonists of the mGlu5 receptor. More specifically, independent Claim 5 claims a compound of formula (1). Reference to page and line numbers in the specification for each group is presented in braces.



(1) **{see page 5, lines 1-4}**

wherin

Ar is 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl,
3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl,
2-cyanophenyl, 3-cyanophenyl, 2-methoxyphenyl, 3-methoxyphenyl,
4-methoxyphenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl,
3,4-difluorophenyl, 3,5-difluorophenyl, 3,4,5-trifluorophenyl,
3-bromophenyl, 3-nitrophenyl, 3-trifluoromethylphenyl, 3-aminophenyl,
3-chloro-4-fluorophenyl, 3-hydroxyphenyl, 3-acetylphenyl, 5-chloro-2-methoxyphenyl,
3-chloro-4-methoxyphenyl, 3-hydroxy-4-fluorophenyl, 3-methoxy-4-fluorophenyl,
3-ethoxy-4-fluorophenyl, 3-isopropoxy-4-fluorophenyl, 3-isopropylphenyl,
3-ethylphenyl, 3-methyl-4-fluorophenyl, 3-trifluoromethyl-4-fluorophenyl,
3-cyano-4-fluorophenyl, 3-amino-4-fluorophenyl,
3-trifluoromethyl-4-fluorophenyl, 3-chloro-4-fluorophenyl,
3-nitro-4-fluorophenyl, 3-aminocarbonyl-4-fluorophenyl,
3-N-methylaminocarbonyl-4-fluorophenyl,
3-N,N-dimethylaminocarbonyl-4-fluorophenyl, 3-carboxyl-4-fluorophenyl,
3-methoxycarbonyl-4-fluorophenyl, 3-acetylaminomethyl-4-fluorophenyl,
3-methysulfonylaminomethyl-4-fluorophenyl,
3-pivaloylaminomethyl-4-fluorophenyl, 3-trifluoromethoxyphenyl,
3-aminomethyl-4-fluorophenyl, 3-dimethylaminomethyl-4-fluorophenyl,

3-cyanomethyl-4-fluorophenyl, 4-fluoro-3-hydroxymethylphenyl,
3-{[(2-cyanoethyl)-methylamino]-methyl}-4-fluorophenyl,
4-fluoro-3-[(isopropylmethylamino)-methyl]phenyl,
4-fluoro-3-isopropylaminomethylphenyl, 4-fluoro-3-propylaminomethylphenyl,
3-ethylaminomethyl-4-fluorophenyl, 4-fluoro-3-methyl aminomethylphenyl, or
3-isobutyrylamino-4-fluorophenyl; **{see page 6, line 15 through page 7, line}**

R^1 is CN, iodo, chloro, methyl or COR^3; **{see page 7, line 22}**

R^2 is 1,2-ethynediyl; and **{see page 7, line 16}**

R^3 is hydrogen or C_1-C_4 alkyl; **{see page 5, line 19}**

or a pharmaceutically acceptable salt thereof; or an N-oxide thereof. **{page 5, line 21}**

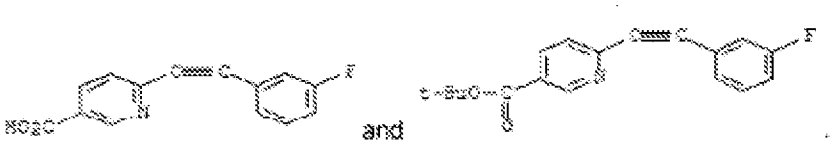
Grounds of Rejection to be Reviewed on Appeal

Whether Claim 5 is unpatentable under 35 U.S.C. §103(a) over Hcaplus 130:124995 in view of Patani et al.

Argument

Prosecution history

In the Office Action of November 26, 2008, the Examiner rejected Claims 5, 10 and 11 under 35 U.S.C. §102(b) as being anticipated by the below two compounds disclosed in Hcaplus 130:124995.



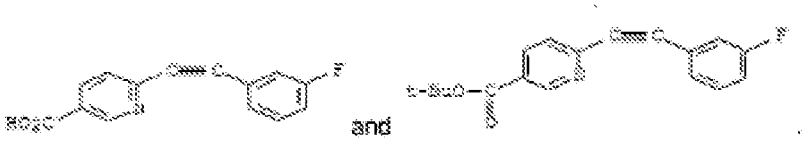
In their reply of Febuary 26, 2009, Appellants traversed the Examiner's rejection:

> Applicants respectfully submit that compounds of the claimed invention are structurally distinct from the two compounds disclosed in the prior art because the compounds of formula 1 require groups which are attached to position 3 and position 5 of the pyridine ring (meta substitution) whereas the two compounds disclosed in Hcaplus 130:124995 require groups which are attached to position 3 and position 6 of the pyridine ring (para substitution). The two compounds disclosed Hcaplus 130:124995 clearly fall outside the scope of the present invention compounds because of these differences in location of the groups relative to each other, as well as the differences in location the groups relative to the nitrogen of the pyridine ring. As such, Claims 5, 10 and 11 are not anticipated by Hcaplus 130:124995.

Also in this response, Appellants provided a copy of the underlying International Patent Application on which the cited prior art, chemical abstract abstract Hcaplus 130:124995, is based:

It is understood Hcaplus 130:124995 is the chemical abstract for WO 99/02497 to Allgeier, Hans et al. published January 21, 1999 for which a copy is provided herewith for the Examiner's convenience.

In the Office Action of June 30, 2009, the Examiner withdrew the rejection under 35 USC §102(b) and issued a new rejection of Claims 5, 10, 11 and 23 under 35 U.S.C. §103(a) as being obvious in view of the aforementioned two compounds disclosed in Hcaplus 130:124995. The Examiner made no reference to Applicants previous submission of WO 99/02497 even though this reference was entered to the applications prior art file. The Examiner provided:

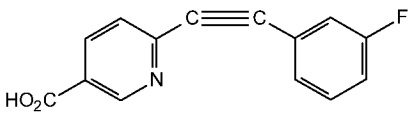


The difference between the prior art compound and the instantly claimed compounds is the placement of the R2Ar moiety on the pyridyl ring. In the prior art compound, the R2Ar moiety is in the ortho position and in the instant compound it is in the meta position. The compounds are used for treating disorders mediated full or in part by mGluR5 as are the instant compounds. The prior art compounds and instant compounds are positional isomers of one another and are similar structurally. Due to the similarity in structure between the prior art compounds and instant compounds and the fact that the instant compounds and compositoins have the same use as the prior art compounds, it would have been obvious to one of ordinary skill in the art to modify the prior art compounds to arrive at the instant compounds. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

In their response of September 29, 2009, Appellants disagreed with the Examiners rejection and amended Claim 5 by incorporating the limitations of dependent Claim 13

where values of R^1 are CN, iodo, chloro, methyl or COR^3. The Examiner had objected to Claim 13 as depending upon a rejected claim. With this amendment to Claim 5, Appellants believed the application was in condition for allowance because Claim 5 now represented non-rejected Claim 13 rewritten in independent form.

In the Office Action of January 25, 2010, the Examiner issued a modified yet final rejection of Claim 5 under 35 U.S.C. §103(a) as being obvious over Hcaplus 130:124995 in view of a newly cited reference, Patani et. al.:

> Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hcaplus 130:124995 in view of Patani et. al. Hcaplus 130:124995 teaches the compound
>
> 
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>
> The difference between the prior art compound and the instantly claimed compounds is the placement of the R2Ar moiety on the pyridyl ring; the second difference is the R1 moiety which in the prior art is carboxyl, but in the instant claims is aldehyde. In the prior art compound, the R2Ar moiety is in the ortho position and in the instant compound it is in the meta position. Patani teaches that that the types of nonclassical biosiosteres used for the replacement of the acidic hydroxyl group of a particular carboxylic acid can be hydrogen. See pages 3154 and page 3168 of Patani et. al. The instant compounds are bioisosteres of the prior art compounds.

The Examiner further provided:

> The prior art compounds and instant compounds are positional isomers of one another, bioisosteres of each other and are similar structurally. Due to the similarity in structure between the prior art compounds and instant compounds and the fact that the instant compounds and compositions [sic] have the same use as the prior

art compounds, it would have been obvious to one of ordinary skill in the art to modify the prior art compounds to arrive at the instant compounds to synthesize bioisosteres of the prior art compounds. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Argument

Appellants assert under 35 U.S.C. §103(a) Claim 5 is patentable over the compound of Hcaplus 130:124995 in view of Patani et al. because the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

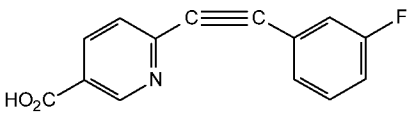
Appellants respectfully submit that one of ordinary skill in the art of medicinal chemistry with knowledge of Hcaplus 130:124995 and Patani et al would not have taken any one of the following steps, let alone the complex combination:

1) selecting the compound of Hcaplus 130:124995 as a lead compound;
2) making the positional isomer of the specific ArR2 group; and
3) substituting the COOH (carboxylic acid) group with a CHO (aldehyde) group

to arrive at a compound of formula 1 of the present invention.

1) No motivation to select the prior art compound of Hcaplus 130:124995 as a lead compound

Appellants respectfully submit the skilled artisan would not be motivated to select



as a lead compound because nothing in Hcaplus 130:124995 or its underlying reference teaches this compound as a starting point to make further modifications.

The United States Court of Appeals for the Federal Circuit has recently explained that within the chemical arts teaching, suggestion or motivation evolves from one of ordinary skill in the art selecting the prior art compound as lead compound to perform further modification, *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.,* 566 F.3d 989 (Fed. Cir 2008):

> An obviousness argument based on structural similarity between claimed and prior art compounds "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." *Takeda*, 492 F.3d at 1359; see also *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (stating that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art).

Appellants respectfully submit a skilled artisan having interest in the content of an abstract would be motivated to seek the text of the underlying document to understand the subject matter as a whole. In the case at hand, a skilled artisan having knowledge of abstract Hcaplus 130:124995 would look to International Patent Application WO 99/02497 for its full teaching including the selection of a compound for further modification.

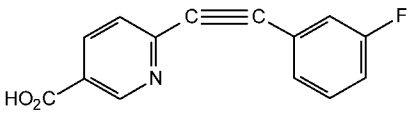
The Examiner chose to rely on the abstract Hcaplus 130:124995 after the Appellants supplied a copy of WO 99/02497 in the response of February 26, 2009. Further, the Examiner chose one specific structure from this abstract while the underlying reference discloses over 350 compounds (see WO 99/02497, the table of Example 7, page 16 to page 28).

Appellants submit the Examiner has erred in relying solely on Hcaplus 130:124995 and not considering the underlying reference WO 99/02497.

> Citation of and reliance upon an abstract without citation of and reliance upon the underlying scientific document is generally inappropriate where both the abstract and the underlying document

are prior art. See *Ex parte Jones*, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001) (unpublished). MPEP §706.02 (II)

Appellants assert nothing in WO 99/02497 suggests the selection of



as a starting point for further modification from the over 350 compounds disclosed. WO 99/02497 teaches preferred compounds and the compound cited by the Examiner is not one that was preferred (see page 7, 2nd paragraph). Appellants assert the Examiner's focus on the selection of this single structure is based on the Appellants invention and not what the reference teaches as a whole. Appellants believe the Examiner has erred in demonstrating the bias of hindsight in selecting this single structure as a starting point for further modification.

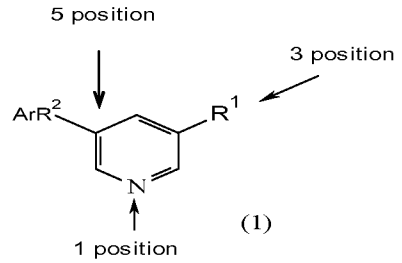
Appellants respectfully submit the skilled artisan would not be motivated to select the cited compound as a lead compound because nothing in the abstract or its underlying reference WO 99/02497 teaches this compound as a starting point to make further modifications.

Appellants assert the skilled artisan with knowledge of Patani would not modify the compound of Hcaplus 130:124995 by making the positional isomer of the specific ArR2 group; and substituting the COOH (carboxylic acid) group with a CHO (aldehyde) to arrive to compounds of the present invention.

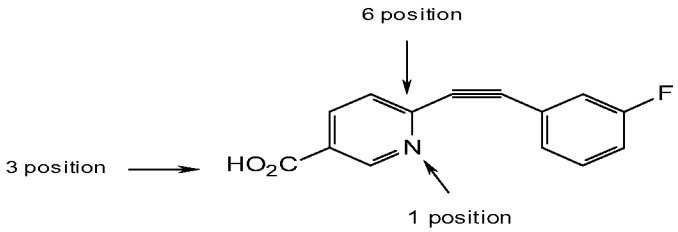
The present invention claims a compound of formula 1 wherein the required groups, R^1 and ArR^2, are attached to position 3 and position 5 of the pyridine ring, respectively. Within the scope of formula 1, a particular value of R^1 is CHO (aldehyde). The compound of Hcaplus 130:124995 requires COOH (carboxylic acid) attached to position 3 and a particular aryl ethynediyl at the position 6 of the pyridine ring (see Figure 1). Thus, the differences in a compound of formula 1 and the compound of Hcaplus 130:124995 are threefold; one, the attachment position of the aryl ethynediyl relative to the pyridine nitrogen wherein there is no longer a carbon spacer; two, the attachment position of the aryl ethynediyl relative to the substituent at position 3 wherein there is now a 2-carbon space rather than a 1-carbon spacer; and three, the nature of the

group at position 3. The present invention includes CHO at position 3 whereas Hcaplus 130:124995 requires this position be COOH.

Figure 1.



Compounds of the present invention R^1 = CHO



Compound of Hcaplus 130:124995

2) No teaching or suggestion to make the positional isomer of the specific ArR2 group.

In the Final Rejection of January 25, 2010, the Examiner stated:

> The prior art compounds and instant compounds are positional isomers of one another, bioisosteres of each other and are similar structurally. Due to the similarity in structure between the prior art compounds and instant compounds and the fact that the instant compounds and compositoins [sic] have the same use as the prior art compounds, it would have been obvious to one of ordinary skill in the art to modify the prior art compounds to arrive at the instant compounds to synthesize bioisosteres of the prior art compounds. (emphasis added)

Appellants respectfully assert the Examiner has erred in concluding that a medicinal chemist reading Patani et al. would modify the position of the ArR^2 group in the compound of Hcaplus 130:124995 to arrive to the Appellants invention. The Examiner has failed to point to any teaching or suggestion in Patani e al. that would motivate a medicinal chemist to make the specific positional group change required to arrive to the claimed invention. More specifically, nowhere does Patani et al. suggest, much less teach, placing the aryl ethynediyl group meta to the pyridine nitrogen, and adding a single carbon spacer between aryl ethynediyl group and the pyridine nitrogen as found in a compound of formula 1 rather than having no spacer as found in the compound of Hcaplus 130:124995.

3) No teaching or suggestion to substitute the COOH (carboxylic acid) group with a CHO (aldehyde) group.

In the Final Rejection of January 25, 2010, the Examiner provided:

> Patani teaches that the types of nonclassical biosiosteres used for the replacement of the acidic hydroxyl group of a particular carboxylic acid can be hydrogen. See pages 3154 and page 3168 of Patani et. al. The instant compounds are bioisosteres of the prior art compounds. (emphasis added)

The Examiner further provided:

> Patani et al. also teaches that the critical component of bioisosterism is that bioisosteres affect the same pharmacological target as agonists or antagonists and thereby, have biological properties which are related to each other.

Appellants respectfully assert the Examiner has erred in concluding that Patani et al. teaches compounds of the present invention are bioisosteres of the compound of Hcaplus 130:124995. Appellants see no teaching or suggestion in the pages referred by the Examiner that the CHO (aldehyde) group of the present invention is a bioisostere of COOH (carboxylic acid).

Appellants submit the Examiner has derived the assertion of bioisosterism from the Appellant's application. Patani et al. teaches the critical component of bioisosterism

is for bioisosteres to have the same pharmacological activity. While the compound of Hcaplus 130:124995 is taught to be an antagonist of mGlu5 receptor, there is no teaching or suggestion in Patani et al. that substituting the art group COOH with the Appellant's group CHO would produce an mGlu5 antagonist. The Examiner could only derive the critical component, mGlu5 antagonist activity for CHO group, from the Appellant's application. Authorities have held the pitfall of hindsight as inappropriate. *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, 381 F.3d 1371 (Fed. Cir. 2004) ("the suggestion to combine references must not be derived by hindsight from knowledge of the invention itself").

Summary

Appellants respectfully submit that one of ordinary skill in the art of medicinal chemistry with knowledge of Hcaplus 130:124995 and Patani et al would not have taken any one of the following steps, let alone the complex combination:

1) selecting the compound of Hcaplus 130:124995 as a lead compound;
2) making the positional isomer of the specific ArR2 group; and
3) substituting the COOH (carboxylic acid) group with a CHO (aldehyde) group

to arrive at the compound of formula 1 of the present invention.

For all of the foregoing reasons, Appellants submit the Examiner's rejection of Claim 5 under 35 U.S.C. §103(a) was in error and should be reversed. Appellants respectfully request reversal of the present rejection and passage of the case to issuance.

Respectfully submitted,

/Mark A. Winter/

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Eli Lilly and Company
Patent Division
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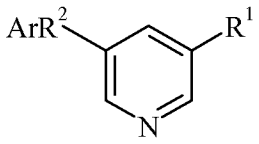
Indianapolis, Indiana 46206-6288
July 22, 2010

Claims Appendix

1. (Withdrawn) A method for treating pain or anxiety in a patient which comprises administering to a patient in need thereof an effective amount of a compound of formula 1:



(1)

wherein

Ar is phenyl or napthyl each of which may be substituted by one or more C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_5 acyl, halo, amino, nitro, cyano, hydroxy, C_1-C_5 acylamino, C_1-C_4 alkylsulfonylamino, mono-, di- or trifluorinated C_1-C_3 alkyl, substituents which may be the same or different and may bear a $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2H, CO_2CH_3, OCF_3, $CH_2NHCOCH_3$, CH_2NH_2, $CH_2N(CH_3)_2$, CH_2CN, CH_2OH, $CH_2NHSO_2CH_3$, $CH_2N(CH_3)(CH_2)_2$ CN, $CH_2N(CH_3)CH(CH_3)_2$, $CH_2NHCH(CH_3)_2$, $CH_2NH(CH_2)_2CH_3$, $CH_2NHCO_2R^4$, $CH_2NHCH_2CH_3$, CH_2NHCH_3, $NHCOC(CH_3)_2$, or $N(S(O)_2CH_3)_2$ substituent;

R^1 is hydrogen, halo, R^4, CN, $C(NOH)R^3$, $C(NO\text{-}R^4)R^3$, $(CH)_2CO_2R^4$, $(CH_2)_n$ OR^3, COR^3, CF_3, SR^4, $S(O)R^4$, $S(O)_2R^4$, $COCH_2CO_2R^3$, $NHSO_2R^4$, $NHCOR^3$,

$C(NOR^3)NH_2$, CH_2OCOR^3, $(CH_2)_n NH_2$, $CON(CH_3)_2$, $(CH_2)_nNHCO_2R^4$, CO_2R^3, $CONH_2$, $CSNH_2$, $C(NH)NHOR^3$, $(CH_2)_nN(CH_3)_2$, or $CONHNHCOR^3$;

R^2 is 1,2-ethenediyl or 1,2-ethynediyl;

R^3 is hydrogen or C_1-C_4 alkyl;

R^4 is C_1-C_4 alkyl; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof; or an N-oxide thereof.

2. (Withdrawn) A method as claimed in Claim 1 wherein

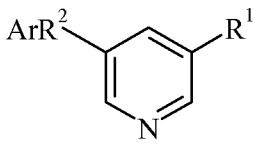
Ar is phenyl or napthyl each of which may be substituted by C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_5acyl, halo, amino, nitro, cyano, hydroxy, C_1-C_5 acylamino, C_1-C_4 alkylsulfonylamino or mono-, di- or trifluorinated C_1-C_3 alkyl; and

R^1 is hydrogen, halo, R^4, CN, $C(NOH)R^3$, $C(NOR^4)R^3$, $(CH)_2CO_2$-R^4, OR^3, COR^3 or CF_3.

3. (Cancelled)

4. (Withdrawn) The method of Claim 1 wherein the patient is a human.

5. (Rejected and on appeal) A compound of formula 1:



(1)

wherein

Ar is 2-chlorophenyl, 3-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl,

3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl,

2-cyanophenyl, 3-cyanophenyl, 2-methoxyphenyl, 3-methoxyphenyl,

4-methoxyphenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl,

3,4-difluorophenyl, 3,5-difluorophenyl, 3,4,5-trifluorophenyl,

3-bromophenyl, 3-nitrophenyl, 3-trifluoromethylphenyl, 3-aminophenyl,

3-chloro-4-fluorophenyl, 3-hydroxyphenyl, 3-acetylphenyl, 5-chloro-2-methoxyphenyl,

3-chloro-4-methoxyphenyl, 3-hydroxy-4-fluorophenyl, 3-methoxy-4-fluorophenyl,

3-ethoxy-4-fluorophenyl, 3-isopropoxy-4-fluorophenyl, 3-isopropylphenyl,

3-ethylphenyl, 3-methyl-4-fluorophenyl, 3-trifluoromethyl-4-fluorophenyl,

3-cyano-4-fluorophenyl, 3-amino-4-fluorophenyl,

3-trifluoromethyl-4-fluorophenyl, 3-chloro-4-fluorophenyl,

3-nitro-4-fluorophenyl, 3-aminocarbonyl-4-fluorophenyl,

3-N-methylaminocarbonyl-4-fluorophenyl,

3-N,N-dimethylaminocarbonyl-4-fluorophenyl, 3-carboxyl-4-fluorophenyl,

3-methoxycarbonyl-4-fluorophenyl, 3-acetylaminomethyl-4-fluorophenyl,

3-methysulfonylaminomethyl-4-fluorophenyl,

3-pivaloylaminomethyl-4-fluorophenyl, 3-trifluoromethoxyphenyl,

3-aminomethyl-4-fluorophenyl, 3-dimethylaminomethyl-4-fluorophenyl,

3-cyanomethyl-4-fluorophenyl, 4-fluoro-3-hydroxymethylphenyl,

3-{[(2-cyanoethyl)-methylamino]-methyl}-4-fluorophenyl,

4-fluoro-3-[(isopropylmethylamino)-methyl]phenyl,

4-fluoro-3-isopropylaminomethylphenyl, 4-fluoro-3-propylaminomethylphenyl,

3-ethylaminomethyl-4-fluorophenyl, 4-fluoro-3-methyl aminomethylphenyl, or 3-isobutyrylamino-4-fluorophenyl;

R^1 is CN, iodo, chloro, methyl or COR^3;

R^2 is 1,2-ethynediyl; and

R^3 is hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof; or an N-oxide thereof.

6 – 13. (Cancelled)

14. The compound of Claim 5 wherein R^1 is CN.

15 – 16. (Cancelled)

17. The compound of Claim 5 wherein R^3 is methyl.

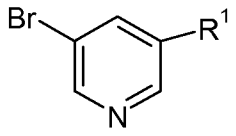
18. The compound Claim 5 wherein R^3 is hydrogen.

19 – 20. (Cancelled).

21. A compound of Claim 5 which is: 5-(4-Fluorophenylethynyl)-nicotinonitrile, 5-(3-Cyanophenylethynyl)-nicotinonitrile or 5-(3,4-difluorophenylethynyl)-nicotinonitrile.

22. A process for preparing a compound of formula 1 (or a pharmaceutically acceptable salt thereof) as provided in Claim 5 which comprises:

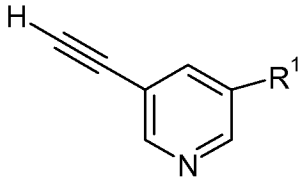
(a) for a compound of formula 1 in which R^2 is 1,2-ethenediyl, reacting with a compound of formula II



(II)

with a compound of formula Ar-$CHCH_2$ in a Heck coupling;

(b) for a compound of formula 1 in which R^2 is alkynyl, reacting with a compound of formula III



(III)

in a Sonogashira coupling with a compound of formula Ar-I or Ar-Br in a suitable solvent;

whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula 1 is required, it is obtained by reacting the basic form of such a compound of formula 1 with an acid affording a physiologically acceptable counterion, or, for a compound of formula 1 which bears an acidic moiety, reacting the acidic form of such a compound of formula 1 with a base which affords a

pharmaceutically acceptable cation, or by any other conventional procedure; and wherein, unless more specifically described, the value of R^1, Ar and R^2 are as defined in Claim 5.

23 - 25. (Cancelled)

26. The compound of Claim 5 which is 5-(3-Chlorophenylethynyl)-nicotinonitrile or a pharmaceutically acceptable salt thereof.

Evidence Appendix

None.

Related Proceedings Appendix

None.